

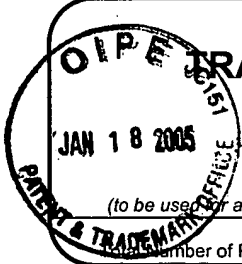
1/19/05

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PTO/SB/21 (09-04)

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# TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Number of Pages in This Submission

18

Application Number

10/700,971

Filing Date

November 4, 2003

First Named Inventor

Muthiah Manoharan

Art Unit

1623

Examiner Name

To Be Determined

Attorney Docket Number

CHEM0005US.P1 (ISIC0009-101)

## ENCLOSURES (Check all that apply)

☐

Fee Transmittal Form

☐

Fee Attached

☐

Amendment/Reply

☐

After Final

☐

Affidavits/declaration(s)

☐

Extension of Time Request

☐

Express Abandonment Request

☒

Information Disclosure Statement

☐

Certified Copy of Priority Document(s)

☐

Reply to Missing Parts/ Incomplete Application

☐

Reply to Missing Parts under 37 CFR 1.52 or 1.53

☐

Drawing(s)

☐

Licensing-related Papers

☐

Petition

☐

Petition to Convert to a Provisional Application

☐

Power of Attorney, Revocation

☐

Change of Correspondence Address

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Terminal Disclaimer

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Request for Refund

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CD, Number of CD(s) \_\_\_\_\_

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Landscape Table on CD

Remarks

☐

After Allowance Communication to TC

☐

Appeal Communication to Board of Appeals and Interferences

☐

Appeal Communication to TC (Appeal Notice, Brief, Reply Brief)

☐

Proprietary Information

☐

Status Letter

☒

Other Enclosure(s) (please identify below):

Forms PTO/SB/08a and PTO/SB/08b (13pp.); Copies of (110) References Cited Enclosed.

## SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm Name

Isis Pharmaceuticals, Inc.

Signature

*Robert S. Andrews*

Printed name

Robert S. Andrews

Date

January 17, 2005

Reg. No.

44,508

## CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below:

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*Kemlyn Evans*

Typed or printed name

Kemlyn Evans

Date

January 17, 2005

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APPLICATION NUMBER: 10/700,971  
FILING DATE: November 4, 2003  
FIRST NAMED INVENTOR: Muthiah Manoharan  
ART UNIT: 1623  
EXAMINER NAME: To Be Determined  
ATTORNEY DOCKET NUMBER: CHEM0005US.P1 (ISIC0009-101)  
TITLE: CONJUGATED OLIGOMERIC  
COMPOUNDS AND THEIR USE IN GENE  
MODULATION

I certify that this communication is being deposited with the U.S. Postal Service in an envelope addressed to Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 utilizing the "Express Mail Post Office to Addresses" service under Mailing Label No. ELO71214675US on the date shown below:

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Robert S. Andrews, Reg. No.44,508

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INFORMATION DISCLOSURE STATEMENT  
Under 37 C.F.R. §§ 1.56 and 1.97-98

SIR:

Pursuant to the provisions of 37 C.F.R. §§ 1.56 and 1.97-98, enclosed herewith is PTO Form PTO/SB/08A and PTO/SB/08B listing references for consideration by the Examiner.

The filing of this Information Disclosure Statement shall not be construed as a representation regarding the completeness of the list of references, or that inclusion of a reference in this list is an admission that it is prior art or is pertinent to this application, or that a search has been made, or as an admission that the information listed is, or may be considered to be, material to patentability, or that no other material information exists, and shall not be construed as an admission against interest in any manner.

This Information Disclosure Statement is being filed:

☒ within three months of the filing date of the application, or date of entry into the national stage of an international application, or before the mailing date of a first office action on the merits, whichever event last occurred;

☐ before the mailing of a first official action after filing of a request for continued examination (RCE) under 37 C.F.R. § 1.114;

☐ after three months of the filing date of this national application or the date of entry of the national stage in an international application, or after the mailing date of the first official action on the merits, whichever event last occurred, but before that mailing date of the first office action to occur of either: (1) a final action under 37 C.F.R. § 1.113; or (2) an action that otherwise closes prosecution in the application, and:

☐ attached hereto is the fee set forth under 37 C.F.R. § 1.17(p) for submission of this Information Disclosure Statement under 37 C.F.R. § 1.97(c); OR

☐ Applicant certifies pursuant to 37 C.F.R. § 1.97(e) that:

☐ each item of the information contained in this Information Disclosure Statement was first cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this Statement;

OR

☐ no item of information contained in this Information Disclosure Statement was cited in a counterpart foreign application and, to the knowledge of the person signing this certification after making reasonable inquiry, no item of information contained in this Statement was known to any individual designated under 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Statement.

☐ on or before the payment of the issue fee but after the mailing date of the first to occur of either: (1) a final action under 37 C.F.R. § 1.113; (2) a notice of allowance under 37 C.F.R. § 1.311; or (3) an action that otherwise closes prosecution in the application, and:

☐ Applicant certifies pursuant to 37 C.F.R. § 1.97(e) that:

☐ each item of information contained in this Information Disclosure Statement was cited in a communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of this statement;

OR

☐ no item of information contained in this Information Disclosure Statement was cited in a counterpart foreign application and, to the knowledge of the person signing this certification after making reasonable inquiry, no item of information contained in this Statement was known to any individual designated under 37 C.F.R. § 1.56(c) more than three months prior to the filing of this Statement. AND

☐ attached hereto is the fee set forth under 37 C.F.R. § 1.17(p) for submission of this Information Disclosure Statement under 37 C.F.R. § 1.97(c); OR

☐ after the payment of the issue fee. Applicant requests that the information contained in this Information Disclosure Statement be placed in the file according to 37 C.F.R. § 1.97(i), although the information may not be considered by the USPTO.

☒ Enclosed is a copy of each listed reference that may be material to the examination of this application, and for which there may be a duty to disclose.

☐ This application relies, under 35 U.S.C. § 120, on the earlier filing date of prior application No. \_\_\_\_\_, filed on \_\_\_\_\_, and the references cited therein are hereby referenced, but are not required to be provided in this application under 37 C.F.R. § 1.98(d).

☒ This application was filed after June 30, 2003. Therefore, pursuant to the waiver of the requirements under 37 C.F.R. § 1.98(a)(2)(i), copies of each U.S. Patent and each U.S. Patent Application Publication are not required to be submitted. Copies of any foreign patent documents and non-patent literature cited herein are enclosed.

☐ Each item of information contained in this Information Disclosure Statement was cited in the communication from a foreign patent office in a counterpart application, and the communication was not received by any individual designated in 37 C.F.R. § 1.56(c) more than thirty days prior to the filing of this Information Disclosure Statement 37 C.F.R. § 1.704(d).

☒ Applicant submits that no fee is required for the consideration of this Information Disclosure Statement.

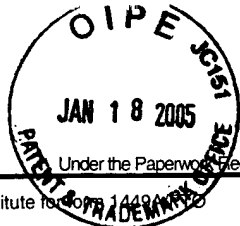
Consideration of the listed references and favorable action are solicited.

Respectively Submitted,

Robert S. Andrews

Robert S. Andrews  
Registration No.: 44,508  
Isis Pharmaceuticals, Inc.  
2292 Faraday Ave.  
Carlsbad, CA 92008

Dated: 1-17-05



Substitute for Form 1449

**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Sheet 1 of 13

**Complete if Known**

Application Number	10/700,971
Filing Date	November 4, 2003
First Named Inventor	Muthiah Manoharan
Art Unit	1623
Examiner Name	To Be Determined
Attorney Docket Number	CHEM0005US.P1 (ISIC0009-101)

**U.S. PATENT DOCUMENTS**

Examiner Initials *	Cite No. <sup>1</sup>	Document Number	Publication/Issue Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code <sup>2</sup> (if known)			
	AA	US-5,898,031	04-27-1999	Crooke	
	AB	US-6,107,094	08-22-2000	Crooke	
	AC	US-6,395,492	05-28-2002	Manoharan	
	AD	US-4,958,013	09-18-1990	Letsinger	
	AE	US-6,528,631	03-04-2003	Manoharan	
	AF	US-4,904,582	02-27-1990	Tullis	
	AG	US-5,672,662	09-30-1997	Harris	
	AH	US-5,714,166	02-03-1998	Tomalia	
	AI	US-6,559,279	05-06-2003	Manoharan	
	AJ	US-6,344,436	02-05-2002	Smith	
	AK	US-6,525,031	02-25-2003	Manoharan	
	AL	US-6,365,379	04-02-2002	Lima	
	AM	US-5,272,250	12-21-1993	Spielvogel	
	AN	US-4,948,882	08-14-1990	Ruth	
	AO	US-5,525,465	06-11-1996	Haralambidis	
	AP	US-5,541,313	07-30-1996	Ruth	
	AQ	US-5,545,730	08-13-1996	Urdea	
	AR	US-5,552,538	09-03-1996	Urdea	
	AS	US-5,580,731	12-03-1996	Chang	
	AT	US-5,486,603	01-23-1996	Buhr	

**FOREIGN PATENT DOCUMENTS**

Examiner Initials *	Cite No. <sup>1</sup>	Foreign Patent Document	Publication Date/Filing Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>
		Country Code <sup>3</sup> - Number <sup>4</sup> - Kind Code <sup>5</sup> (if known)				
	AU	✓ WO 01/48183	07-05-2001	Devgen NV		
	AV	✓ WO 00/44895	08-03-2000	Kreutzer		
	AW	✓ WO 00/49035	08-24-2000	General Hospital		
	AX	✓ WO 00/63364	10-26-2000	American Home Products Corp.		
	AY	✓ WO 01/36641	05-25-2001	Chiron Corp.		
	AZ	✓ WO 01/36646	05-25-2001	Cancer Research		
	BA	✓ WO 99/32619	07-01-1999	Carnegie Inst. Of Washington		
	BB	✓ WO 00/44914	08-03-2000	Med. College of Georgia		
	BC	✓ WO 01/29058	04-26-2001	Univ. of Mass.		

Examiner  
SignatureDate  
Considered

\*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant. <sup>1</sup> Applicant's unique citation designation number (optional). <sup>2</sup> See Kinds Codes of USPTO Patent Documents at [www.uspto.gov](http://www.uspto.gov) or MPEP 901.04. <sup>3</sup> Enter Office that issued the document, by the two-letter code (WIPO Standard ST.3). <sup>4</sup> For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. <sup>5</sup> Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST. 16 if possible. <sup>6</sup> Applicant is to place a check mark here if English language Translation is attached.

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Substitute for form 1449A/PTO  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  <i>(Use as many sheets as necessary)</i>			<b>Complete if Known</b>		
			Application Number	10/700,971	
			Filing Date	November 4, 2003	
			First Named Inventor	Muthiah Manoharan	
			Art Unit	1623	
			Examiner Name	To Be Determined	
			Attorney Docket Number	CHEM0005US.P1 (ISIC0009-101)	
Sheet	2	of	13		

U.S. PATENT DOCUMENTS					
Examiner Initials *	Cite No. <sup>1</sup>	Document Number	Publication/Issue Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code <sup>2</sup> (if known)			
	BD	US-5,608,046	03-04-1997	Cook	
	BE	US-4,587,044	05-06-1986	Miller	
	BF	US-4,667,025	05-19-1987	Miyoshi	
	BG	US-5,254,469	10-19-1993	Warren	
	BH	US-5,245,022	09-14-1993	Weis	
	BI	US-5,112,963	05-12-1992	Pieles	
	BJ	US-5,391,723	02-21-1995	Priest	
	BK	US-5,510,475	04-23-1996	Agrawal	
	BL	US-5,512,667	04-30-1996	Reed	
	BM	US-5,574,142	11-12-1996	Meyer	
	BN	US-5,684,142	11-04-1997	Mishra	
	BO	US-5,770,716	06-23-1998	Khan	
	BP	US-6,096,875	08-01-2000	Khan	
	BQ	US-6,335,432	01-01-2002	Segev	
	BR	US-6,335,437	01-01-2002	Manoharan	
	BS	US-4,828,979	05-09-1989	Klevan	
	BT	US-5,218,105	06-08-1993	Cook	
	BU	US-5,578,717	11-26-1996	Urdea	
	BV	US-5,591,584	01-07-1997	Chang	
	BW	US-5,109,124	04-28-1992	Ramachandran	

FOREIGN PATENT DOCUMENTS						
Examiner Initials *	Cite No. <sup>1</sup>	Foreign Patent Document	Publication Date/Filing Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T <sup>6</sup>
		Country Code <sup>3</sup> - Number <sup>4</sup> - Kind Code <sup>5</sup> (if known)				
	BX	✓ WO 01/75164	10-11-2001	Whitehead Inst.		
	BY	✓ WO 93/07883	04-29-1993	Isis Pharm.		
	BZ	✓ WO 00/76554	12-21-2000	Isis Pharm.		
	CA	✓ WO 96/11205	04-18-1996	Isis Pharm.		
	CB	WO 98/52614	11-26-1998	Brd. Of Trustees of the Leland Stanford Junior Univ.		

Examiner Signature		Date Considered	
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Substitute for form 1449A/PTO  <b>INFORMATION DISCLOSURE STATEMENT BY APPLICANT</b>  <i>(Use as many sheets as necessary)</i>				<b>Complete if Known</b>	
				Application Number	10/700,971
				Filing Date	November 4, 2003
				First Named Inventor	Muthiah Manoharan
				Art Unit	1623
				Examiner Name	To Be Determined
				Attorney Docket Number	CHEM0005US.P1 (ISIC0009-101)
Sheet	3	of	13		

U.S. PATENT DOCUMENTS					
Examiner Initials *	Cite No. <sup>1</sup>	Document Number	Publication/Issue Date MM-DD-YYYY	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number - Kind Code <sup>2</sup> (if known)			
	CC	US-5,118,802	06-02-1992	Smith	
	CD	US-5,138,045	08-11-1992	Cook	
	CE	US-5,414,077	05-09-1995	Lin	
	CF	US-5,512,439	04-30-1996	Hornes	
	CG	US-5,578,718	11-26-1996	Cook	
	CH	US-4,605,735	08-12-1986	Miyoshi	
	CI	US-4,762,779	08-09-1988	Snitman	
	CJ	US-4,789,737	12-06-1988	Miyoshi	
	CK	US-4,824,941	04-25-1989	Gordon	
	CL	US-4,835,263	05-30-1989	Nguyen	
	CM	US-4,876,335	10-24-1989	Yamane	
	CN	US-5,082,830	01-21-1992	Brakel	
	CO	US-5,214,136	05-25-1993	Lin	
	CP	US-5,149,782	09-22-1992	Chang	
	CQ	US-5,258,506	11-02-1993	Urdea	
	CR	US-5,262,536	11-16-1993	Hobbs	
	CS	US-5,292,873	03-08-1994	Rokita	
	CT	US-5,317,098	05-31-1994	Shizuya	
	CU	US-5,371,241	12-06-1994	Brush	
	CV	US-5,416,203	05-16-1995	Letsinger	

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		Country Code <sup>3</sup> - Number <sup>4</sup> - Kind Code <sup>5</sup> (if known)				

Examiner Signature		Date Considered	
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**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**

(Use as many sheets as necessary)

Sheet 4 of 13

**Complete if Known**

Application Number	10/700,971
Filing Date	November 4, 2003
First Named Inventor	Muthiah Manoharan
Art Unit	1623
Examiner Name	To Be Determined
Attorney Docket Number	CHEM0005US.P1 (ISIC0009-101)

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		Number - Kind Code <sup>2</sup> (if known)			
	CW	US-5,451,463	09-19-1995	Nelson	
	CX	US-5,514,785	05-07-1996	Van Ness	
	CY	US-5,565,552	10-15-1996	Magda	
	CZ	US-5,567,810	10-22-1996	Weis	
	DA	US-5,585,481	12-17-1996	Arnold	
	DB	US-5,587,371	12-24-1996	Sessler	
	DC	US-5,595,726	01-21-1997	Magda	
	DD	US-5,597,696	01-28-1997	Linn	
	DE	US-5,599,923	02-04-1997	Sessler	
	DF	US-5,599,928	02-04-1997	Hemmi	
	DG	US-5,688,941	11-18-1997	Cook	
	DH	US-6,153,737	11-28-2000	Manoharan	
	DI	US-6,172,208	01-09-2001	Cook	
	DJ	US-6,300,319	10-09-2001	Manoharan	
	DK	US-6,335,434	01-01-2002	Guzaev	
	DL	US-6,395,437	05-28-2002	Wollesen	
	DM	US-6,444,806	09-03-2002	Veerapaneni	
	DN	US-6,486,308	11-26-2002	Kutyavin	

**FOREIGN PATENT DOCUMENTS**

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		Country Code <sup>3</sup> - Number <sup>4</sup> - Kind Code <sup>5</sup> (if known)				

Examiner  
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**INFORMATION DISCLOSURE  
STATEMENT BY APPLICANT**

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Sheet 5 of 13

**Complete if Known**

Application Number	10/700,971
Filing Date	November 4, 2003
First Named Inventor	Muthiah Manoharan
Art Unit	1623
Examiner Name	To Be Determined
Attorney Docket Number	CHEM0005US.P1 (ISIC0009-101)

**NON PATENT LITERATURE DOCUMENTS**

Examiner Initials *	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
	DO	AFONINA, I. et al., "Sequence-specific arrest of primer extension on single-stranded DNA by an oligonucleotide-minor groove binder conjugate," <i>Proc. Natl. Acad. Sci. USA</i> (1996) 93:3199-3204.	
	DP	ANTOPOLSKY, M. et al., "Peptide-Oligonucleotide Phosphorothioate Conjugates with Membrane Translocation and Nuclear Localization Properties," <i>Bioconjugate Chem.</i> (1999) 10(4):598-606.	
	DQ	ARAR, K. et al., "Synthesis and Antiviral Activity of Peptide-Oligonucleotide Conjugates Prepared by Using Na-(Bromoacetyl)peptides," <i>Bioconjugate Chem.</i> (1995) 6(5):573-577.	
	DR	ASSELIN, U. et al., "Nucleic acid-binding molecules with high affinity and base sequence specificity: Intercalating agents covalently linked to oligodeoxynucleotides," <i>Proc. Natl. Acad. Sci. USA</i> (1984) 81:3297-3301.	
	DS	ASTRIAB-FISHER, A. et al., "Antisense Inhibition of P-glycoprotein Expression Using Peptide-Oligonucleotide Conjugates," <i>Biochem. Pharmacol.</i> (2000) 60:83-90.	
	DT	BAKER, B. F. et al., "Oligonucleotide-europium complex conjugate designed to cleave the 5' cap structure of the ICAM-1 transcript potentiates antisense activity in cells," <i>Nucleic Acids Res.</i> (1999) 27(6):1547-1551.	
	DU	BOLLIG, F. et al., "Affinity purification of ARE-binding proteins identifies poly(A)-binding protein 1 as a potential substrate in MK2-induced mRNA stabilization," <i>Biochem. Biophys. Res. Commun.</i> (2003) 301:665-670.	
	DV	BONGARTZ, J.-P. et al., "Improved biological activity of antisense oligonucleotides conjugated to a fusogenic peptide," <i>Nucleic Acids Res.</i> (1994) 22(22):4681-4688.	
	DW	BONORA, G. M. et al., "Biological Properties of Antisense Oligonucleotides Conjugated to Different High-Molecular Mass Poly(Ethylene Glycols)," <i>Nucleosides Nucleotides</i> (1999) 18(6&7):1723-1725.	
	DX	BONORA, G. M. et al., "Antisense activity of an anti-HIV oligonucleotide conjugated to linear and branched high molecular weight polyethylene glycols," <i>Farmaco</i> (1998) 53:634-637.	
	DY	BOUTLA, A. et al., "Short 5'-phosphorylated double-stranded RNAs induce RNA interference in <i>Drosophila</i> ," <i>Curr. Biol.</i> (2001) 11:1776-1780.	

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Sheet 6 of 13

**Complete if Known**

Application Number	10/700,971
Filing Date	November 4, 2003
First Named Inventor	Muthiah Manoharan
Art Unit	1623
Examiner Name	To Be Determined
Attorney Docket Number	CHEM0005US.P1 (ISIC0009-101)

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	DZ	BRANDEN, L. J. et al., "A peptide nucleic acid-nuclear localization signal fusion that mediates nuclear transport of DNA," <i>Nature Biotech</i> (1999) 17:784-787.	
	EA	BRANTL, S., "Antisense-RNA regulation and RNA interference," <i>Biochimica et Biophysica Acta</i> (2001) 1575:15-25.	
	EB	CAZALLA, D. et al., "Nuclear Export and Retention Signals in the RS Domain of SR Proteins," <i>Mol. Cell. Biol.</i> (2002) 22(19):6871-6882.	
	EC	CHALOIN, L. et al., "Design of Carrier Peptide-Oligonucleotide Conjugates with Rapid Membrane Translocation and Nuclear Localization Properties," <i>Biochem. Biophys. Res. Commun.</i> (1998) 243:601-608.	
	ED	CHIANG, M.-Y. et al., "Antisense Oligonucleotides Inhibit Intercellular Adhesion Molecule I Expression by Two Distinct Mechanisms," <i>J. Biol. Chem.</i> (1991) 266(27):18162-18171.	
	EE	CHIU, Y.-L. et al., "RNAi in Human Cells: Basic Structural and Functional Features of Small Interfering RNA," <i>Molecular Cell</i> (2002) 10:549-561.	
	EF	COGONI, C. et al., "Post-transcriptional gene silencing across kingdoms," <i>Genes Dev.</i> (2000) 10:638-643.	
	EG	COHEN, G. L. et al., "Sequence Dependent Binding of <i>cis</i> -Dichlorodiammineplatinum(II) to DNA," <i>J. Am. Chem. Soc.</i> (1980) 102(7):2487-2488.	
	EH	COREY, D. R., "48000-fold Acceleration of Hybridization by Chemically Modified Oligonucleotides," <i>J. Am. Chem. Soc.</i> (1995) 117(36):9373-9374.	
	EI	COREY, D. R. et al., "Generation of a Hybrid Sequence-Specific Single-Stranded Deoxyribonuclease," <i>Science</i> (1987) 238:1401-1403.	
	EJ	COREY, D. R. et al., "Sequence-Selective Hydrolysis of Duplex DNA by an Oligonucleotide-Directed Nuclease," <i>J. Am. Chem. Soc.</i> (1989) 111(22):8523-8525.	

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Application Number	10/700,971
Filing Date	November 4, 2003
First Named Inventor	Muthiah Manoharan
Art Unit	1623
Examiner Name	To Be Determined
Attorney Docket Number	CHEM0005US.P1 (ISIC0009-101)

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	EK	DUFF, R. J. et al., "[17] Intrabody Tissue-Specific Delivery of Antisense Conjugates in Animals: Ligand-Linker-Antisense Oligomer Conjugates," <i>Methods Enzymol.</i> (2000) 313:297-321.	
	EL	EFIMOV, V. A. et al., "Synthesis of Polyethylene Glycol - Oligonucleotide Conjugates," <i>Bioorg. Khim.</i> (1993) 19(8):800-804.	
	EM	ELBASHIR, S. M. et al., "RNA interference is mediated by 21- and 22-nucleotide RNAs," <i>Genes Dev.</i> (2001) 15:188-200.	
	EN	ELBASHIR, S. M. et al., "Duplexes of 21-nucleotide RNAs mediate RNA interference in cultured mammalian cells," <i>Nature</i> (2001) 411:494-498.	
	EO	ELBASHIR, S. M. et al., "Functional anatomy of siRNAs for mediating efficient RNAi in <i>Drosophila melanogaster</i> embryo lysate," <i>EMBO J.</i> (2001) 20(23):6877-6888.	
	EP	FIRE, A. et al., "Potent and specific genetic interference by double-stranded RNA in <i>Caenorhabditis elegans</i> ," <i>Nature</i> (1998) 391:806-811.	
	EQ	FIRESTONE, R. A., "Low-Density Lipoprotein as a Vehicle for Targeting Antitumor Compounds to Cancer Cells," <i>Bioconjugate Chem.</i> (1994) 5:105-113.	
	ER	GORLACH, M. et al., "The mRNA Poly(A)-Binding Protein: Localization, Abundance, and RNA-Binding Specificity," <i>Exp. Cells Res.</i> (1994) 211:400-407.	
	ES	GUO, S. et al., " <i>par-1</i> , a Gene Required for Establishing Polarity in <i>C. elegans</i> Embryos, Encodes a Putative Ser/Thr Kinase That Is Asymmetrically Distributed," <i>Cell</i> (1995) 81:611-620.	
	ET	GURA, T., "A silence that speaks volumes," <i>Nature</i> (2000) 404:804-808.	
	EU	GUZAEV, A. et al., "Conjugation of Oligonucleotides Via an Electrophilic Tether: N-Chloroacetamidohexyl Phosphoramidite Reagent," <i>Bioorg. Med. Chem. Lett.</i> (1998) 8:3671-3676.	

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Sheet 8 of 13

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Application Number	10/700,971
Filing Date	November 4, 2003
First Named Inventor	Muthiah Manoharan
Art Unit	1623
Examiner Name	To Be Determined
Attorney Docket Number	CHEM0005US.P1 (ISIC0009-101)

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	EV	HALL, J. et al., "Efficient sequence-specific cleavage of RNA using novel europium complexes conjugated to oligonucleotides," <i>Chem. Biol.</i> (1994) 1(3):185-190.	
	EW	HARITON-GAZAL, E. et al., "Targeting of Nonkaryophilic Cell-Permeable Peptides into the Nuclei of Intact Cells by Covalently Attached Nuclear Localization Signals," <i>Biochemistry</i> (2002) 41(29):9208-9214.	
	EX	HENDERSON, B. R. et al., "A Comparison of the Activity, Sequence Specificity, and CRM1-Dependence of Different Nuclear Export Signals," <i>Exp. Cell Res.</i> (2000) 256:213-224.	
	EY	HUANG, L. et al., "Oligonucleotide conjugates of Eu(III) tetraazamacrocycles with pendent alcohol and amide groups promote sequence-specific RNA cleavage," <i>J. Biol. Inorg. Chem.</i> (2000) 5:85-92.	
	EZ	HUH, N. et al., "Design, Synthesis, and Evaluation of Mitomycin-Tethered Phosphorothioate Oligodeoxynucleotides," <i>Bioconjugate Chem.</i> (1996) 7:659-669.	
	FA	JASCHKE, A. et al., "Synthesis and properties of oligodeoxyribonucleotide-polyethylene glycol conjugates," <i>Nucleic Acids Res.</i> (1994) 22(22):4810-4817.	
	FB	JORGENSEN, R. A. et al., "Chalcone synthase cosuppression phenotypes in petunia flowers: comparison of sense vs. antisense constructs and single-copy vs. complex T-DNA sequences," <i>Plant Mol. Biol.</i> (1996) 31:957-973.	
	FC	JUBY, C. D. et al., "Facile Preparation of 3'Oligonucleotide-Peptide Conjugates," <i>Tetrahedron Letters</i> (1991) 32(7):879-882.	
	FD	KABANOV, A. V. et al., "A new class of antivirals: antisense oligonucleotides combined with a hydrophobic substituent effectively inhibit influenza virus reproduction and synthesis of virus-specific proteins in MDCK cells," <i>FEBS Lett.</i> (1990) 259(2):327-330.	
	FE	KRIEG, A. M. et al., "Uptake of Oligodeoxyribonucleotides by Lymphoid Cells Is Heterogeneous and Inducible," <i>Antisense Research and Development</i> (1991) 1:161-171.	
	FF	KUIJPERS, W. H. A. et al., "Specific Recognition of Antibody-Oligonucleotide Conjugates by Radiolabeled Antisense Nucleotides: A Novel Approach for Two-Step Radioimmunotherapy of Cancer," <i>Bioconjugate Chem.</i> (1993) 4(1):94-102.	

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			Application Number	10/700,971	
			Filing Date	November 4, 2003	
			First Named Inventor	Muthiah Manoharan	
			Art Unit	1623	
			Examiner Name	To Be Determined	
Sheet	9	of	13	Attorney Docket Number	CHEM0005US.P1 (ISIC0009-101)

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	FG	LETSINGER, R. L. et al., "Cholesteryl-conjugated oligonucleotides: Synthesis, properties, and activity as inhibitors of replication of human immunodeficiency virus in cell culture," <i>Proc. Natl. Acad. Sci. USA</i> (1989) 86:6553-6556.	
	FH	LI, S. et al., "Folate-Mediated Targeting of Antisense Oligodeoxynucleotides to Ovarian Cancer Cells," <i>Pharm. Res.</i> (1998) 15(10):1540-1545.	
	FI	LIMA, W. F. et al., "Highly efficient endonucleolytic cleavage of RNA by a Cys2His2 zinc-finger peptide," <i>Proc. Natl. Acad. Sci. USA</i> (1999) 96:10010-10015.	
	FJ	LIN, M. et al., "Inhibition of collagenase type I expression by psoralen antisense oligonucleotides in dermal fibroblasts," <i>Faseb J.</i> (1995) 9:1371-1377.	
	FK	LIN, K.-Y. et al., "A Cytosine Analogue Capable of Clamp-Like Binding to a Guanine in Helical Nucleic Acids," <i>J. Am. Chem. Soc.</i> (1998) 120(33):8531-8532.	
	FL	LIPARDI, C. et al., "RNAi as Random Degradative PCR: siRNA Primers Convert mRNA into dsRNAs that Are Degraded to Generate New siRNAs," <i>Cell</i> (2001) 107:297-307.	
	FM	LIU, K. et al., "Efficient Nuclear Delivery of Antisense Oligodeoxynucleotides and Selective Inhibition of CETP Expression by Apo E Peptide in a Human CETP-Stably Transfected CHO Cell Line," <i>Arterioscler. Thromb. Vasc. Biol.</i> (1999) 19:2207-2213.	
	FN	LIXIN, R. et al., "Novel Properties of the Nucleolar Targeting Signal of Human Angiogenin," <i>Biochem. Biophys. Res. Comm.</i> (2001) 284:185-193.	
	FO	LUKHTANOV, E. A. et al., "Direct, Solid Phase Assembly of Dihydropyrroloindole Peptides with Conjugated Oligonucleotides," <i>Bioconjugate Chem.</i> (1996) 7(5):564-567.	
	FP	MANOHARAN, M., "Oligonucleotide Conjugates in Antisense Technology," <i>Antisense Drug Technology, Principles, Strategies, and Applications</i> , Crooke, S. T. ed., Marcel Dekker, New York, (2001) Chapter 16, 391-467.	
	FQ	MANOHARAN, M. et al., "Novel Functionalization of the Sugar Moiety of Nucleic Acids for Multiple Labeling in the Minor Groove," <i>Tetrahedron Letters</i> (1991) 32(49):7171-7174.	

Examiner Signature		Date Considered	
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Sheet 10 of 13

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Application Number	10/700,971
Filing Date	November 4, 2003
First Named Inventor	Muthiah Manoharan
Art Unit	1623
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	FR	MANOHARAN, M., "Oligonucleotide Conjugates as Potential Antisense Drugs with Improved Uptake, Biodistribution, Targeted Delivery and Mechanism of Action," <i>Antisense &amp; Nucleic Acid Drug Development</i> (2002) 12:103-128.	
	FS	MANOHARAN, M., "Designer Antisense Oligonucleotides: Conjugation Chemistry and Functionality Placement," <i>Antisense Research and Applications</i> , Crooke and Lebleu, eds., CRC Press Boca Raton, FL (1993) Chapter 17, 303-349.	
	FT	MANOHARAN, M. et al., "Lipidic Nucleic Acids," <i>Tetrahedron Lett.</i> (1995) 36(21):3651-3654.	
	FU	MARTINEZ, J. et al., "Single-Stranded Antisense siRNAs Guide Target RNA Cleavage in RNAi," <i>Cell</i> (2002) 110:563-574.	
	FV	MARUENDA, H. et al., "Antisense Sequence-Directed Cross-Linking of DNA Oligonucleotides by Mitomycin C," <i>Bioconjugate Chem.</i> (1996) 7(5):541-544.	
	FW	MARUENDA, H. et al., "Antisense sequence-directed cross-linking of RNA oligonucleotides by mitomycin," <i>Anti-Cancer Drug. Des.</i> (1997) 12:473-479.	
	FX	MELLITZER, G. et al., "Spatial and temporal 'knock down' of gene expression by electroporation of double-stranded RNA and morpholinos into early postimplantation mouse embryos," <i>Mechanisms of Development</i> (2002) 118:57-63.	
	FY	MEUNIER, L. et al., "The nuclear export signal-dependent localization of oligonucleopeptides enhances the inhibition of the protein expression from a gene transcribed in cytosol," <i>Nucleic Acids Res.</i> (1999) 27(13):2730-2736.	
	FZ	MILI, S. et al., "Distinct RNP Complexes of Shuttling hnRNP Proteins with Pre-mRNA and mRNA: Candidate Intermediates in Formation and Export of mRNA," <i>Mol. Cell Biol.</i> (2001) 21(21):7307-7319.	
	GA	MISHRA, R. K. et al., "Improved leishmanicidal effect of phosphorothioate antisense oligonucleotides by LDL-mediated delivery," <i>Biochim. Biophys. Acta.</i> (1995) 1264:229-237.	
	GB	MONTGOMERY, M. K. et al., "RNA as a target of double-stranded RNA-mediated genetic interference in <i>Caenorhabditis elegans</i> ," <i>Proc. Natl. Acad. Sci. USA</i> (1998) 95:15502-15507.	

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Sheet 11 of 13

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Application Number	10/700,971
Filing Date	November 4, 2003
First Named Inventor	Muthiah Manoharan
Art Unit	1623
Examiner Name	To Be Determined
Attorney Docket Number	CHEM0005US.P1 (ISIC0009-101)

**NON PATENT LITERATURE DOCUMENTS**

Examiner Initials *	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>2</sup>
	GC	NAPOLI, C. et al., "Introduction of a Chimeric Chalcone Synthase Gene into Petunia Results in Reversible Co-Suppression of Homologous Genes <i>in trans</i> ," <i>Plant Cell</i> (1990) 2:279-289.	
	GD	NELSON, P. S. et al., "Bifunctional oligonucleotide probes synthesized using a novel CPG support are able to detect single base pair mutations," <i>Nucleic Acids Res.</i> (1989) 17(18):7187-7194.	
	GE	NISHIKURA, K. et al., "A Short Primer on RNAi: RNA-Directed RNA Polymerase Acts as a Key Catalyst," <i>Cell</i> (2001) 107:415-418.	
	GF	OBERHAUSER, B. et al., "Effective incorporation of 2'-O-methyl-oligoribonucleotides into liposomes and enhanced cell association through modification with thiocholesterol," <i>Nucleic Acids Res.</i> (1992) 20(3):533-538.	
	GG	PARRISH, S. et al., "Functional Anatomy of a dsRNA Trigger: Differential Requirement for the Two Trigger Strands in RNA Interference," <i>Molecular Cell</i> (2000) 6:1077-1087.	
	GH	PICHON, C. et al., "Intracellular Routing and Inhibitory Activity of Oligonucleopeptides Containing a KDEL Motif," <i>Mol. Pharmacol.</i> (1997) 51:431-438.	
	GI	PRAKASH, T. P. et al., "Synthesis of Site-Specific Oligonucleotide-Polyamine Conjugates," <i>Bioorg. Med. Chem. Lett.</i> (1994) 4(14):1733-1738.	
	GJ	RAJUR, S. B. et al., "Covalent Protein-Oligonucleotide Conjugates for Efficient Delivery of Antisense Molecules," <i>Bioconjugate Chem.</i> (1997) 8(6):935-940.	
	GK	RHODES, J. et al., "Therapeutic potentiation of the immune system by costimulatory Schiff-base-forming drugs," <i>Nature</i> (1995) 377(6544):71-75.	
	GL	RUMP, E. T. et al., "Preparation of Conjugates of Oligodeoxynucleotides and Lipid Structures and Their Interaction with Low-Density Lipoprotein," <i>Bioconjugate Chem.</i> (1998) 9(3):341-349.	
	GM	SAISON-BEHMOARAS, T. et al., "Short modified antisense oligonucleotides directed against Ha-ras point mutation induce selective cleavage of the mRNA and inhibit T24 cells proliferation," <i>EMBO J.</i> (1991) 10(5):1111-1118.	

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	GN	SCHWARZ, D. S. et al., "Evidence that siRNAs Function as Guides, Not Primers, in the <i>Drosophila</i> and Human RNAi Pathways," <i>Molecular Cell</i> (2002) 10:537-548.	
	GO	SHEA, R. G. et al., "Synthesis, hybridization properties and antiviral activity of lipid-oligodeoxynucleotide conjugates," <i>Nucleic Acids Res.</i> (1990) 18(13):3777-3783.	
	GP	SIJEN, T. et al., "On the Role of RNA Amplification in dsRNA-Triggered Gene Silencing," <i>Cell</i> (2001) 107:465-476.	
	GQ	SVINARCHUK, F. P. et al., "Inhibition of HIV proliferation in MT-4 cells by antisense oligonucleotide conjugated to lipophilic groups," <i>Biochimie</i> (1993) 75:49-54.	
	GR	TABARA, H. et al., "RNAi in <i>C. elegans</i> : Soaking in the Genome Sequence," <i>Science</i> (1998) 282:430-431.	
	GS	TAMANINI, F. et al., "The fragile X-related proteins FXR1P and FXR2P contain a functional nucleolar-targeting signal equivalent to the HIV-1 regulatory proteins," <i>Hum. Mol. Genet.</i> (2000) 9(10):1487-1493	
	GT	TIJSTERMAN, M. et al., "RNA Helicase MUT-14-Dependent Gene Silencing Triggered in <i>C. elegans</i> by Short Antisense RNAs," <i>Science</i> (2002) 295:694-697.	
	GU	TIMMONS, L. et al., "Specific interference by ingested dsRNA," <i>Nature</i> (1998) 395:854.	
	GV	TIMMONS, L. et al., "Ingestion of bacterially expressed dsRNAs can produce specific and potent genetic interference in <i>Caenorhabditis elegans</i> ," <i>Gene</i> (2001) 263:103-112.	
	GW	TUSCHL, T. et al., "Targeted mRNA degradation by double-stranded RNA in vitro," <i>Genes Dev.</i> (1999) 13:3191-3197.	
	GX	WADA, A. et al., "Nuclear export of actin: a novel mechanism regulating the subcellular localization of a major cytoskeletal protein," <i>EMBO J.</i> (1998) 17:1635-1641.	

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	GY	WANG, X. et al., "Modular Recognition of RNA by a Human Pumilio-Homology Domain," <i>Cell</i> (2002) 110:501-512.	
	GZ	WEI, Z. et al., "Hybridization properties of oligodeoxynucleotide pairs bridged by polyarginine peptides," <i>Nucleic Acids Res.</i> (1996) 24(4):655-661.	
	HA	WEIN, G. et al., "The 3'-UTR of the mRNA coding for the major protein kinase C substrate MARCKS contains a novel CU-rich element interacting with the mRNA stabilizing factors HuD and HuR," <i>Eur. J. Biochem.</i> (2003) 270:350-365.	
	HB	YANG, Y. et al., "HIV-1 TAT-mediated protein transduction and subcellular localization using novel expression vectors," <i>FEBS Letters</i> (2002) 532:36-44.	
	HC	ZANTA, M. A. et al., "Gene delivery: A single nuclear localization signal peptide is sufficient to carry DNA to the cell nucleus," <i>Proc. Natl. Acad. Sci. USA</i> (1999) 96:91-96.	
	HD	ZHANG, Z. et al., "Uptake of N-(4'-pyridoxyl)amines and release of amines by renal cells: A model for transporter-enhanced delivery of bioactive compounds," <i>Proc. Natl. Acad. Sci. USA</i> (1991) 88:10407-10410.	
	HE	ZHU, T. et al., "Oligonucleotide-Poly-L-ornithine Conjugates: Binding to Complementary DNA and RNA," <i>Antisense Res. Dev.</i> (1993) 3:265-275.	
	HF	ZUCKERMANN, R. N. et al., "Site-Selective Cleavage of RNA by a Hybrid Enzyme," <i>J. Am. Chem. Soc.</i> (1988) 110:1614-1615.	

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